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PREPARATION OF STABLE HYDROPHILIC ASPIRIN OINTMENT
[Anteina Shinsuisei Assupirin Nanko No Chosei]

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1. Introduction /502[1]

We previously prepared 2% aspirin ointment (oily[1)], hydrophilic ointment[2)], oral[3)]) and have clarified that this ointment was clinically effective as an external pain-killer of neuralgia after zoster[1,4,5)], clinic articular rheumatism[2)], and oral endermosis[3,6)].

In the hydrophilic ointment used in the clinic articular rheumatism, the ointment was spread and rubbed on an affected part, and a pain disappeared after several minutes, and the pain alleviation duration time reached even 8 h. Also, it has been clarified that the effect was stronger than that of indomethacin ointment and a cold sense type poultice[2)]. On the other hand, in the hydrophilic ointment, even after 60 days in storing it in a cold place (5°C), the aspirin was stable (99.9%), however in storing it at 20°C and 30°C, the aspirin tended to be slowly decomposed with a lapse of time[2)]. For this reason, it was necessary to store it in a cold place (5°C) and to return to room temperature before using and instruct a patient to spread and rub it. Accordingly, the purpose of this paper is to prepare a hydrophilic ointment in which an aspirin is also stable at room temperature, and the base and the amount of moisture are reviewed.

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[1]Numbers in the margin indicate pagination in the foreign text.

Experiment

1. Sample

An aspirin (based on the Japanese Pharmacy Law, made by Hoei Yakko K.K.) was used as a main drug, and as an ointment base, hydrogenated rape-seed oil (made by Floint Sangyo K.K.) and isopropyl myristate (chemical, made by Wako Pure Chemical Industries, Ltd.) were used. As a surfactant, glycerin monostearate (based on the Japanese Pharmacy Law, made by Niko Chemicals K.K.) and polyoxyethylene hydrogenated castor oil 60[7] (out of the Japanese Pharmacy Law, made by Floint Sangyo K.K.) were used, and as a dissolver, crotamiton[8] (out of the Japanese Pharmacy Law, made by Aldrich) and isopropanol (special grade, made by Komune Kagaku Yakuhin K.K.) were used. Furthermore, in order to stabilize aspirin, a salicylic acid (based on the Japanese Pharmacy Law, made by Maruishi Seiyaku K.K.) was used, and as a dehydrator, a molecular sieve 4A (made by Wako Pure Chemical Industries, Ltd.) was used. /503

2. Kind of formulation

Prescriptions of the aspirin ointment prepared were shown in Table I. In the prescription 1, a conventional hydrophilic ointment[2] was prepared, and in the prescription 2, a salicylic acid as a hydrolyzed product of an aspirin was added to the prescription 1. In the prescription 3, a polyoxyethylene hydrogenated castor oil 60 was added to the prescription 1 instead of the glycerin monostearate, and in the prescription 4, a salicylic acid was added to the prescription 3. In the

prescription 5, an isopropanol was used as a dissolver instead of the crotamiton of the prescription 3. The reason why the amount of isopropanol of the prescription 5 is smaller than the previous prescription[2] is that a specific odor of the isopropanol is reduced.

Table 1. Formula of 2% Aspirin Ointment

Rp. 1	Aspirin	2 g	Rp. 2	Aspirin	2 g
	Crotamiton	6 g		Salicylic Acid	0.2 g
	Hydrogenated			Crotamiton	6 g
	Rape Seed Oil	30 g		Hydrogenated	
	MGS-ASE*	5 g		Rape Seed Oil	30 g
	Isopropyl Myristate	ad 100 g		MGS-ASE*	5 g
				Isopropyl Myristate	ad 100 g
Rp. 3	Aspirin	2 g	Rp. 4	Aspirin	2 g
	Crotamiton	6 g		Salicylic Acid	0.2 g
	Hydrogenated			Crotamiton	6 g
	Rape Seed Oil	30 g		Hydrogenated	
	HCO-60**	5 g		Rape Seed Oil	30 g
	Isopropyl Myristate	ad 100 g		HCO-60**	5 g
				Isopropyl Myristate	ad 100 g
Rp. 5	Aspirin	2 g			
	Isopropanol	5 g			
	Hydrogenated				
	Rape Seed Oil	30 g			
	HCO-60**	5 g			
	Isopropyl Myristate	ad 100 g			

* MGS-ASE : Glyceryl Monostearate

** HCO-60 : Polyoxyethylenehydrogenated Castor Oil 60

3. Preparation method

Similarly to the conventional hydrophilic ointment[2], first, an aspirin raw powder is sampled by a mortar, and a dissolver is added to it and sufficiently stirred. In the prescriptions 2 and 4, a salicylic acid is added to it. Furthermore, a hydrogenated rape-seed oil and a glycerin monostearate or polyoxyethylene hydrogenated castor oil 60 are added to a mortar separately

heated with warm water in advance, dissolved on a warm bath by heating, and cooled, and an isopropyl myristate was slowly added little by little to it and triturated. Then, the above-mentioned aspirin dissolved solution is added to it and sufficiently stirred and kneaded until the entire portion becomes homogenous and uniform.

4. Measurement of stability

(1) Storage condition: The ointment was put into an ointment container made of a plastic and stored at 5°C, 20°C, and 30°C.

(2) Observation period: Right after preparing the ointment, it was observed for 1 day, 7 days, 14 days, 21 days, and 56 days.

As an incubator, a taper type electric low-temperature /504 incubator (Hirazawa Seisakusho) was used.

(3) Measuring method: 20 mg ointment was precisely weighed, and an average value was attained from a four-time measurement by a HPLC method similar to that of the previous report[9]. In the method, using an isopanol containing a 3,4-dimethylbenzoic acid as an internal standard substance, an aspirin was extracted from the ointment, separated (eluant: 40% aqueous acetonitrile solution containing 0.1% trifluoroacetic acid) by a reversed-phase column (TSK)ODS80T_M), detected at a detection wavelength of 237 nm, and the residual amount of aspirin was quantified.

5. Measurement of the amount of moisture

The amount of moisture in each drug and ointment was measured by Karl Fischer technique[10] based on the Japanese Pharmacy Law. As the measurement conditions, a chloroform-

methanol solution (1:1) as a solvent, a factor (the amount of moisture per 1 ml Karl Fischer reagent) of 5.328 mg/ml, a terminal interval of 20 sec, and a S-TIMER (dissolution wait time) of 2-10 min were used. As a measuring apparatus, a Hirazawa moisture measurer AQV-5SP (capacity method, single burette) was used.

Results and consideration

Five kinds of hydrophilic aspirin ointments in which hydrogenated rape-seed oil, glycerin monostearate (MGS-ASE), polyoxyethylene hydrogenated castor oil 60 (HCO-60), and isopropyl myristate were used as the base and crotamiton or isopropanol was used as the dissolver were prepared. The reason why the salicylic acid was added in the prescriptions 2 and 4 was considered that the hydrolysis of the aspirin was suppressed by adding an acid (L.J. Edwards reported that the most stable pH of the aspirin was about 2.5[11,12]) and the decomposition of the aspirin was suppressed by adding the salicylic acid as a decomposed product of the aspirin in advance, so that a further stabilization might be realized. The reason why the glycerin monostearate of the prescriptions 1 and 2 was replaced with the polyoxyethylene hydrogenated castor oil 60 like the prescriptions 3 and 4 was that it was anticipated that the glycerin monostearate had a large amount of moisture. The reason why the dissolver was changed from the crotamiton to the isopropanol in the prescription 5 was that the isopropanol dissolved was stable in the previous report[2]. In the preparation, the amount of odor

was reduced up to the degree that it was not felt. Also, since moisture[13] was considered as a factor having an influence on the stability of the aspirin, the amount of moisture in the ointment was measured.

1. Stability of aspirin in the ointments

When the aspirin content right after the preparation in five kinds of ointment prescriptions was assumed as 100%, the residual rate of the aspirin was shown in Figures 1-5.

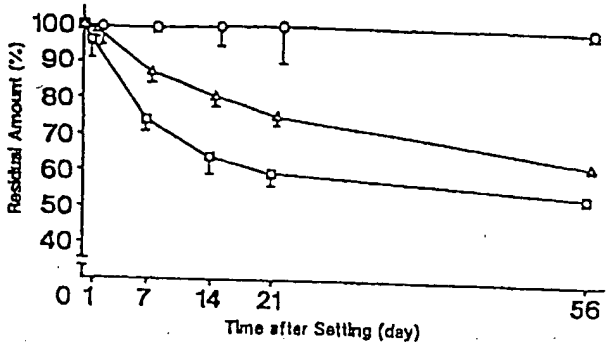

Fig. 1. Time Course of Degradation of Aspirin in 2% Aspirin Ointment (Rp. 1) at 5°C, 20°C and 30°C
The determination was made by HPLC.
○—○ : at 5°C, △—△ : at 20°C, □—□ : at 30°C
Each point represents mean ±S.E. (n =4).

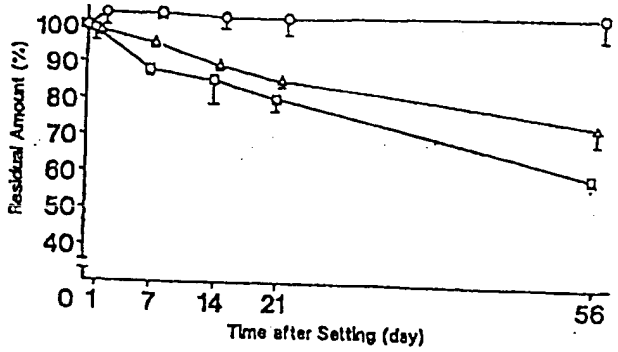

Fig. 2. Time Course of Degradation of Aspirin in 2% Aspirin Ointment Containing 0.2 % Salicylic Acid (Rp. 2) at 5°C, 20°C and 30°C
The determination was made by HPLC.
○—○ : at 5°C, △—△ : at 20°C, □—□ : at 30°C
Each point represents mean ±S.E. (n =4).

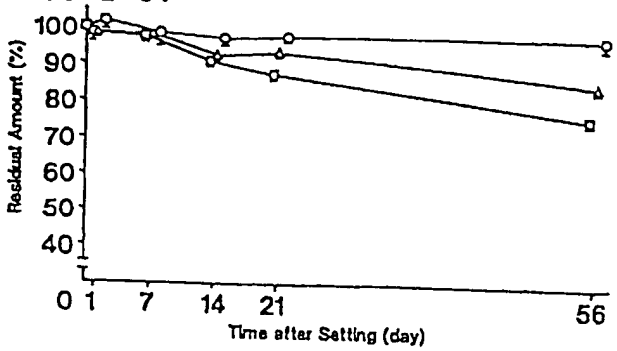

Fig. 3. Time Course of Degradation of Aspirin in 2% Aspirin Ointment Including HCO-60 Instead of MGS-ASE (Rp. 3) at 5°C, 20°C and 30°C
The determination was made by HPLC.
○—○ : at 5°C, △—△ : at 20°C, □—□ : at 30°C
Each point represents mean ±S.E. (n =4).

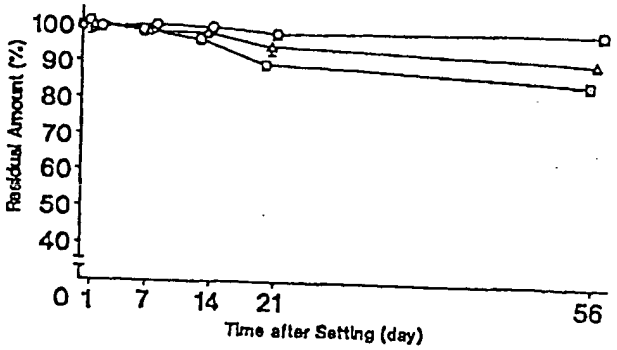

Fig. 4. Time Course of Degradation of Aspirin in 2% Aspirin Ointment Including HCO-60 Instead of MGS-ASE, and also Containing 0.2% Salicylic Acid (Rp. 4) at 5°C, 20°C and 30°C
The determination was made by HPLC.
○—○ : at 5°C, △—△ : at 20°C, □—□ : at 30°C
Each point represents mean ±S.E. (n =4).

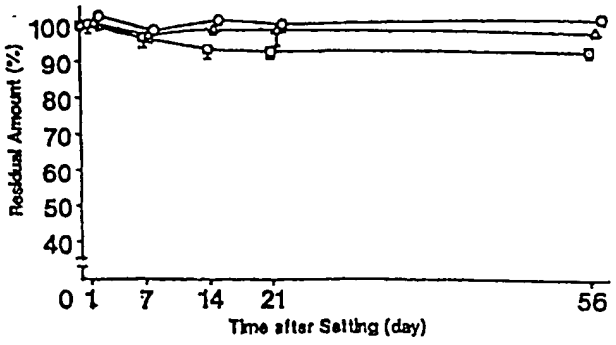

Fig. 5. Time Course f Degradation of Aspirin in 2% Aspirin Ointment Including Isopropanol and HCO-60 Instead of Crotamiton and MGS-ASE, Respectively (Rp.5) at 5°C, 20°C and 30°C
The determination was made by HPLC.
o—o : at 5°C, △—△ : at 20°C, □—□ : at 30°C
Each point represents mean ±S.E. (n =4).

In all five kinds of ointments, the residual amount was /505 seldom changed at 5°C up to 56 days. At 20°C and 30°C, a tendency in which the aspirin was slowly decomposed with a lapse of time was recognized. It was recognized that the decomposition suppression effect due to the acidic additive (salicylic acid) used to suppress the hydrolysis of the aspirin was not sufficient (Figures 1 and 2 and Figures 3 and 4). Also, it was recognized that the decomposition was suppressed by replacing the glycerin monostearate with the polyoxyethylene hydrogenated castor oil 60 (Figures 1 and 3 and Figures 2 and 4). Furthermore, the stability was further increased by using the isopropanol instead of the crotamiton (Figure 5).

When the half life of the aspirin in each ointment was calculated from these data on the assumption that the decomposition rate was a first-order reaction, the half life at 20°C was 80 days in the prescription 1, 128 days in the prescription 2, 250 days in the prescription 3, 428 days in the

prescription 4, and 2,004 days in the prescription 5. The half life at 30°C was 53 days in the prescription 1, 76 days in the prescription 2, 144 days in the prescription 3, 229 days in the prescription 4, and 501 days in the prescription 5.

From the above facts, of the hydrophilic aspirin ointments prepared in this paper, the ointment (prescription 5) prepared with the polyoxyethylene hydrogenated castor oil 60 by dissolving with the isopropanol was a very stable ointment with a residual rate of 98.2% at 20°C and 92.5% at 30°C, even after 56 days. From the above results, it was considered that this ointment could be stored at room temperature instead of storing in a cold place (5°C) and could be used as a pain killer for a clinic articular rheumatism.

2. Amount of moisture of the ointment base

It was considered that the results might be due to the difference in the amount of moisture being included in the ointment base.

As shown in Table II, the hydrogenated rape-seed oil and /506 the isopropyl myristate have a relatively small amount of moisture, however the glycerin monostearate as the surfactant has an amount of moisture greater than that of the polyoxyethylene hydrogenated castor oil 60. Also, the polysorbate 80 and the crotamiton used as the dissolver of the aspirin have an amount of moisture greater than that of the isopropanol. This is a difference in the amount of moisture in the base. It is considered that such a difference results in the difference in

the aspirin stability of the aspirin ointments.

Table 2. Water Content of Materials and Ointments

	Sample			(%) n=4
1)	Hydrogenated Rape Seed Oil			0.1068±0.008
2)	Isopropyl Myristate			0.0311±0.001
3)	Glyceryl Monostearate (MGS-ASE)			2.9250±0.277
4)	Polyoxyethylenehydrogenated Castor Oil 60 (HCO-60)			2.2560±0.152
5)	Polysorbate 80			3.1045±0.029
6)	Carmellose Sodium (CMC-Na)			3.4020±0.257
7)	Isopropanol			0.0117±0.004
8)	Isopropanol (+Molecular Sieves)			0.0082±0.001
9)	Isopropanol (+2% Anhydrous Sodium Sulfate)			0.0131±0.001
10)	Crotamiton			0.1838±0.002
11)	Crotamiton (+Molecular Sieves)			0.0161±0.001
12)	Crotamiton (+2% Anhydrous Sodium Sulfate)			0.1825±0.003
13)	Crotamiton (dehydrated*)			0.0436±0.003
14)	Crotamiton	6 g		
	Hydrogenated Rape Seed Oil	30 g		
	MGS-ASE	5 g		
	Isopropyl Myristate	ad. 100 g		0.3240±0.043
15)	Crotamiton	6 g		
	Hydrogenated Rape Seed Oil	30 g		
	HCO-60	5 g		
	Isopropyl Myristate	ad. 100 g		0.2273±0.076
16)	Isopropanol	5 g		
	Hydrogenated Rape Seed oil	30 g		
	HCO-60	5 g		
	Isopropyl Myristate	ad. 100 g		0.1727±0.061
17)	Polysorbate 80	5 ml		
	Plastibase	ad. 100 g		0.2850±0.031
18)	Carmellose Sodium	20 g		
	Plastibase	ad. 100 g		0.7332±0.052
19)	Hydrogenated Rape Seed Oil	30 g	}	
	MGS-ASE	5 g	} (dehydrated*)	
	Isopropyl Myristate	ad. 100 g	}	0.0441±0.006
20)	Hydrogenated Rape Seed Oil	30 g	}	
	HCO-60	5 g	} (dehydrated*)	
	Isopropyl Myristate	ad. 100 g	}	0.0492±0.018
21)	Aspirin			0.0179±0.005

* dehydrated : under vacuum for several hours

3. Relationship between the half life and the amount of moisture of aspirin of the ointments

When the relationship between the half life of the aspirin in 2% aspirin ointment (oily[1], hydrophilic ointment[2], oral[3]) /507 and the amount of moisture of Table II was plotted, it was clarified that the smaller amount of moisture in the ointment, the longer is the half life of the aspirin (the higher is the stability) (Figure 6). However, the oral aspirin ointment was exceptional, and although the moisture content was large, the aspirin was relatively stable. The reason for this is considered that the base is a fat and oil, the amount of moisture in the carmellose sodium (CMC-Na) used as an oral tackifier, most of the total moisture is included in the CMC-Na, and the CMC-Na restricts a free water.

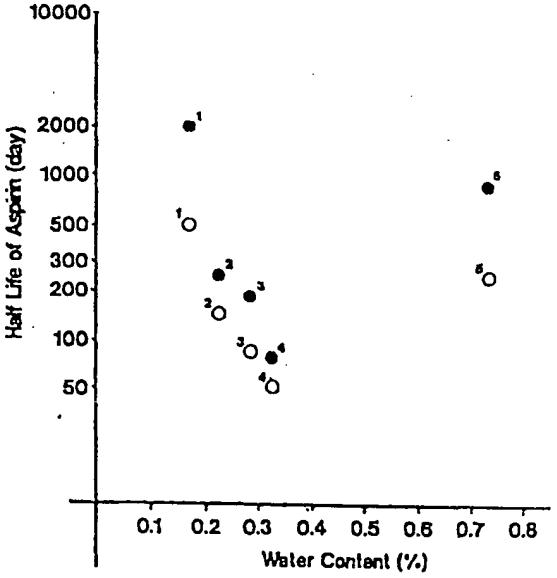

Fig. 6. Relation between Water Content of Ointment and Stability of Aspirin in 2% Aspirin Ointment

1. Isopropanol + Hydrogenated Rape Seed Oil + HCO-60 + Isopropyl Myristate (Rp. 5)
2. Crotamiton + Hydrogenated Rape Seed Oil + HCO-60 + Isopropyl Myristate (Rp. 3)
3. Polysorbate 80 + Plastibase
4. Crotamiton + Hydrogenated Rape Seed Oil + MGS-ASE + Isopropyl Myristate (Rp. 1)
5. CMC-Na + Plastibase

● : 20°C, ○ : 30°C

From Figure 6, it can be predicted that if moisture is extremely reduced from the ointment, a stable aspirin ointment can be formed. Accordingly, the dissolvers were dehydrated with a molecular sieve (Table II, Nos. 8 and 11), and using the ointment bases (Table II, Nos. 19 and 20) absorbed by a vacuum pump, the ointments (corresponding to Figures 1 and 5) of the prescriptions 1 and 5 were prepared.

As expected, the half life of the aspirin of these ointments was further prolonged (Figures 7 and 8). At that time, the half life at 20°C was 306 days in the prescription 1 (Figure 7) and 2,248 days in the prescription 5 (Figure 8), and the half life at 30°C was 169 days in the prescription 1 (Figure 7) and 928 days /508 in the prescription 5 (Figure 8).

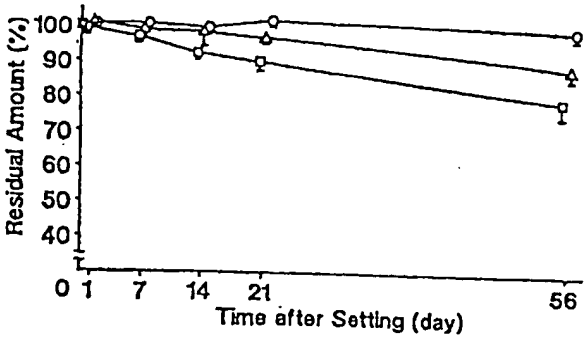

Fig. 7. Time Course of Degradation of Aspirin in 2% Aspirin Ointment Containing Dehydrated Ingredients (Rp. 1) at 5°C, 20°C and 30°C
The determination was made by HPLC.
○—○ : at 5°C, △—△ : at 20°C, □—□ : at 30°C
Each point represents mean ±S.E. (n =4).

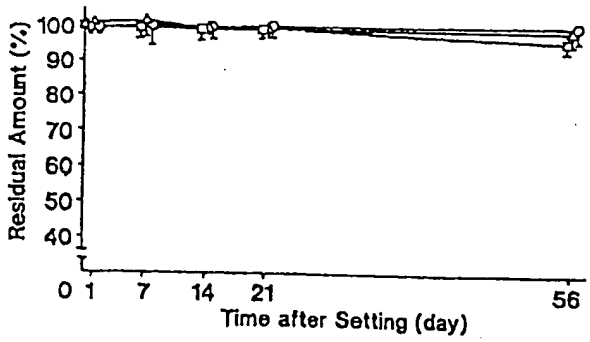

Fig. 8. Time Course of Degradation of Aspirin in 2% Aspirin Ointment Containing Dehydrated Ingredients (Rp. 5) at 5°C, 20°C and 30°C
The determination was made by HPLC.
○—○ : at 5°C, △—△ : at 20°C, □—□ : at 30°C
Each point represets mean ± S.E. (n =4).

From the above facts, in the review of the base, it was recognized that with the replacement of the glycerin monostearate with the polyoxyethylene hydrogenated castor oil 60 having a small amount of moisture and the change of the dissolver of the aspirin from the crotamiton to the isopropanol, the aspirin in the ointment base was stabilized. Furthermore, the prescription 5 of Table I finally prepared was pharmaceutically stable for 2 months, even at room temperature. Furthermore, it was found out that with the reduction of the amount of moisture in the base, the aspirin of the ointment could be further stabilized. As a result, it is considered that the aspirin ointment being generally broadly used as well as nosocomial formulations can be formulated.

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